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Dear Lederberg,

Thank you for your letter of March 26, which reached me two days ago. I have sent a letter to Hayes, of which I enclose a copy, because he might already have sent his paper + or ~~be intending~~ to send it very soon to the editors of JGM, and on further delay publication on the same issue might become impossible. Thank you for your news re origin of resistance; I hope the reprint will reach me in time.

The problem of F+ effect on segregation is fascinating, but rather difficult to explain on current hypotheses. I have tested the asymmetry of segregations, analogous to that I described in my earlier letter, also in the reversed crosses (i.e. * $TLB_1$-$S^r$sugars + x $TLB_1$+sugars -, F+ x F- and F- x F+) ; it is almost superimposable on the preceding one. F+ x F+ crosses are somewhat intermediate, occasionally with some bias in one or other sense ( which may be in agreement with your scheme of relative sexuality) i.e. resembling more one than the other of the two corresponding F+ x F- , F- x F+ crosses. Asymmetry is also found in BM- x W 945, F+ x F- and F- x F+ ; F+ x F+ intermediate. I have found myself testing mentally the wildest hypotheses. It may be that the F+ parent contributes a "shorter" chromosome - but I am now favoring the idea that the F+ "gamete" carries a single strand, while the F- gamete carries more than one (polytenic or multinuclear ?) and that crossing-over can happen repeatedly before segregation. However, even if the system behaved as a multivalant, with a single round of crossing-over, it might explain the elimination of the contribution from the F+ parent, subject to the restrictions due to the markers. You are in a much better position with Het, where no fixed markers need being employed. Could the data obtained from the Het segregations be explained assuming that fertilization results from the union of a haploid (F+) gamete with a polyploid (F-) one, and that a multivalent is formed.

I have no new data on Hfr; I have never tested attenuated strains, but shall do so . I shall test more crosses Hfr x x $TLB_1$-F+ to see if the differences I have found in behaviour reappear, and send you the relevant cultures.

Re Mrs. Lederberg's question on NCTC 123 : it was possible to grow 123 on minimal + methionine + lysine, and thus select a few auxotrophs (a leucineless, and a threonineless): additional sugar and virus markers were added . A mixture of the auxotrophs, or the separate auxotrophs (on methionine + Lysine) gave

* preceding one may $TLB_1$-$S^r$sugars - x $TLB_1$+sugars +

When I tried again in Milan to grow the original strain on MLy, I coul never get any growth out of it. Almost all derivatives of 123 were los ~~in the~~ when I moved from Cambridge to Milan .123 is a poor grower; it may have been lost/even at the British NCTC - at least thus told me Weigle. I am very glad to hear that Mrs.Lederberg has succeeded in doing something out of it ; I have felt bitter against this strain for some time and am anxious/to hear if she can confirm my rather scanty experience about its self-incompatibility .I never succeeded in getting prototrophs out of it. Do they keep the original small colony type ? An interesting remark about colony size is that while all recombinants from 123 x bm-Nfr were small-sized, there was a segregation for size when crossing 123 to Hfr.

I shall let you have as soon as written ,the short paper for the local Microbiology congress,which I shall be glad to give as a joi paper with the Lederbergs. I hope you can manage reading Italian ; it may amuse you,for once, to try and understand it .

Yours sincerely

Cavalli-